EAG Erratum - Early Value Assessment: Genedrive MT-RNR1 ID Kit for detecting single nucleotide polymorphism m.1555A>G in neonates

Produced by Newcastle Technology Assessment Review Group

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Corrections to the Assessment Report

1. Scientific summary conclusion has been amended to provide further discussion of the results. The original conclusion appeared on page 11.
2. The word ‘rare’ was changed to ‘relatively uncommon’. This error appeared on page 13.
3. Information regarding other variants that might cause AIHL have been added. The original text appeared on page 14.
4. Table 20 and Table 21 have been amended. These errors appeared on page 55.
5. Table 22 and some associated text has been amended. These errors appeared on page 56-57.
6. Addition of new references and references 17 and 18 swapped and addition of two references added after stakeholder comments. Original reference list appeared from page 71.
7. The second study in the reference list was incorrect and has been replaced with the correct reference. This error appeared on page 84.

Results

The evidence to inform this EVA was extremely limited, only one study was included in the clinical effectiveness rapid review for which risk of bias was rated as being moderate for most of the outcomes measured.

The included study suggested high diagnostic test accuracy (Sensitivity = 100%, Specificity = 99.2%). Estimates of sensitivity were very uncertain, due to a small number of positive cases (i.e. people with the m.1555A>G variant) but no false negatives were identified. However, there were some false positives (n = 5 of 8), the specificity estimate was very high with sufficient precision.

This was established from 424 successful tests, with a test failure rate of 17.1% (90 patients). The failure rate was reduced to 5.1% in repeated testing of samples post after modifications were made to the assay buffer and the test cartridge was redesigned. Overall, three neonates were identified with the genetic variant. The trial research team were able to genotype the m.1555A>G variant using the Genedrive MT-RNR1 ID Kit in 26 minutes. Time to antibiotics when using the Genedrive MT-RNR1 ID Kit did not differ from normal practice (i.e. not using the test kit). Difference between groups was not statistically significant (mean difference=-0.87 minutes, 95% CI: -5.96 to 4.23 minutes) and the 95% CI was within the predefined boundary for statistical equivalence.

We did not identify any studies that reported on the following intermediate, clinical or patient related outcomes: impact of test implementation and use on healthcare resources, , usability of the test, mortality and morbidity. Additionally, no studies assessed the usage of the point of care test in mothers.

No relevant economic evaluations were identified. From the conceptual economic model key evidence gaps were identified. These include the sensitivity of the Genedrive MT-RNR1 ID Kit for identifying the gene m.1555A>G variant in neonates, the magnitude of risk for aminoglycoside induced hearing loss (AIHL) in neonates and mothers with m.1555A>G, and the prevalence of the gene m.1555A>G variant. Other potential important gaps include how data regarding maternal inheritance may potentially be used in the clinical pathway. The early health economic model focused on some of those parameters, where on consideration of the available data, the estimates of cost-effectiveness would be most sensitive to changes. The results of this model showed that the use of the Genedrive MT-RNR1 ID Kit for identification of the m.1555A>G genetic variant could potentially be cost-effective. In a deterministic sensitivity analysis, the results were shown to be most sensitive to changes in the time horizon, the sensitivity of the Genedrive MT-RNR1 ID Kit system, the proportion of neonates with m.1555A>G variant suffering from AIHL after being exposed to aminoglycosides and the prevalence of the m.1555A>G variant in the UK population.

Conclusions

There is limited evidence for the assessment of the Genedrive MT-RNR1 ID Kit for identification of the m.1555A>G genetic variant. Overall, the results suggest that the Genedrive MT-RNR1 ID Kit has promise as an accurate point of care test. Additionally, it potentially could provide rapid identification of neonates with the m.1555A>G genetic variant within a time sensitive period for antibiotic usage. However, the test was conducted in two large NICUs and thus may not be generalisable to smaller NICUs or other hospitals. Therefore, the usage of the Genedrive MT-RNR1 Kit should be investigated further in varying settings. Furthermore, while there were modifications made to the Kit to reduce failure rate, when used in the clinical setting this was not completely eradicated. There were no existing economic evaluations that addressed this topic. The total cost per test to the NHS was estimated to be £130, however there is uncertainty surrounding this.

1. Background and definition of decision problem

1.1 Background to decision problem

Infection can develop into sepsis, which is the body's potentially life-threatening response to an infection. Sepsis and bacterial infections are significant causes of mortality and morbidity in neonates (up to and including 28 days corrected gestational age). Expert opinion suggests the incidence of culture-confirmed neonatal infection is around 1 in 2,000 deliveries. But a larger proportion of babies will go on to receive precautionary antibiotic treatment for suspected infection. For example, approximately 30 to 60 of every 1,000 blood culture samples taken in Neonatal Intensive Care Units (NICUs) 2020-2022 were positive.[1]

1.1.1 Prevalence of m.1555A>G variant and risk of aminoglycoside-induced hearing loss (AIHL)

Neonates with suspected infection are commonly treated with gentamicin, an antibiotic of the aminoglycoside family. These antibiotics are associated with a very high risk of damage to the ear (ototoxicity), including profound bilateral deafness, in people with the MT-RNR1 gene m.1555A>G mitochondrial variant.[2, 3]

The prevalence of the variant in a number of cohort studies is relatively uncommon. For example in the UK, Rahman and colleagues have found similar prevalence rates of m. 1555A>G in two representative samples of the UK Population: the Avon Longitudinal Study of Parents And Children (ALSPAC), 0.19% (95% CI 0.10 to 0.28, 18/9371 participants);[4] and the 1958 Birth Cohort study, 0.26% (95% CI 0.14% to 0.38%, 19/7350 participants).[5] This is approximately 1 in 400/500 neonates. According to the UK Rare Diseases Framework, a rare condition affects fewer than 1 in 2000 people. Hence, using this number as a reference, it can be inferred that the variant is not very common.

Given these low prevalence rates, it is unsurprising AIHL has been investigated primarily in case-control studies, in families who have experienced hearing impairment due to maternal inheritance of the m.1555A>G variant. These studies have found all people exposed to aminoglycosides experienced hearing loss.[2, 3] However, these study designs are likely to overestimate the risk of aminoglycoside exposure. Cohort studies of hearing loss in people with the m.1555A>G genetic variant in broader populations (e.g. preterm infants, neonates in NICUs not selected on the basis of existing hearing impairment) have suggested greater uncertainty on the risk of AIHL.

A German study of preterm infants found only three of ten infants with the m.1555A>G variant, and exposed to aminoglycosides, failed the newborn hearing screening test.[6] Two American studies conducted in NICUs also suggest not all infants with the variant, and exposed to aminoglycosides, experienced hearing loss. Ealy et al 2011 identified two infants with the m.1555A>G genetic variant who received aminoglycosides. Both passed their newborn hearing screening test. Johnson et al 2010 identified three infants with the m.1555A>G genetic variant, all were exposed to aminoglycosides. Only one of these infants failed their newborn hearing screening test.

However, these studies also have multiple limitations. For example, later hearing loss due to neonatal exposure to aminoglycosides cannot be ruled out in those infants who passed newborn hearing screening tests. In addition, these studies are based on very small samples of people with the m.1555A>G variant. Therefore, there is substantial uncertainty regarding how many neonates with the m.1555A>G variant and exposed to aminoglycosides are likely to experience hearing loss.

1.1.2 1555A>G variant and nonsyndromic hearing loss (without exposure to aminoglycosides)

The prevalence of nonsyndromic hearing loss in people with the m.1555A>G variant is a further uncertainty.

Case control studies in people with the m.1555A>G genetic variant experiencing hearing impairment, suggest AIHL may not explain all hearing impairment in these populations. For example, one Spanish study found that 65% (45/69) of families who carried the variant experienced hearing impairment despite no exposure to aminoglycosides.[2] In another case control study of 70 Spanish families, Estivill et al[3] estimated that 39.9% of carriers of the variant, without exposure to aminoglycosides, still experienced hearing loss. However, they found a much lower median age for hearing loss (5 years) in those treated with aminoglycosides compared to those not treated with aminoglycosides (20 years).

As above, case-control studies may overestimate the risk of nonsyndromc hearing loss. For example, no evidence of hearing loss was found in people with the m.1555A>G variant in two UK population cohort studies conducted by Rahman and colleagues.[4, 5] However, no data on aminoglycoside use were available and the sample size of people with the variant was small in both studies. The Australian Blue Mountains Hearing Study had contrasting findings. Six participants (total sample size = 2,856 participants) identified with the m.1555A>G variant all experienced hearing loss, yet none reported aminoglycoside use. After statistical adjustment, three of six carriers of the m.1555A>G variant were found to have mean auditory thresholds higher than the general population.

It is also worth noting that in addition to m.1555A>G, many other MT-RNR1 variants (i.e. m.1095T>C and m.1494C>T) have been proposed as being associated with AIHL. However, most of the evidence stems from single studies and thus there is insufficient evidence to support their risk for AIHL.

1.1.3 Maternal inheritance of m.1555A>G variant

The m.1555A>G variant, since it is a variant of mitochondrial DNA (mtDNA), is inherited maternally. Mitochondrial DNA variants are commonly heteroplasmic (when mtDNA varies widely within the same cell and mitochondrion). Therefore, most children have similar but not identical mtDNA to their mothers and other maternal relatives. However, some mitochondrial variants are homoplasmic (when all or most copies are identical throughout mtDNA), resulting in greater penetrance of the variant.

Most studies of this variant have found people are homoplasmic for the G allele (for example, Matsunaga et al).[7] However, people with a heteroplasmic variant have been identified in several studies including in Spanish families with m.1555A>G and hearing impairment,[8] and a large genetic screening study (24,349 neonates) in a Chinese hospital.[9] Del Castillo et al found in six families there were 19 people with heteroplasmy for the variant and 12 people with the variant in homoplasmy.[8] The proportion of variant copies differed widely in the heteroplasmic participants (3.75% - 96.60%). Although Del Castillo et al found correlations between variant load and hearing thresholds, the small sample size makes these data difficult to interpret. Luo et al found that most neonates (39/46 people)with m.1555A>G were homoplasmic and 7/46 people heteroplasmic.[8]

For the prevalence of the m.1555A>G variant, the high and low values used in the sensitivity analysis were the 95% confidence intervals from Bitner-Glindzicz *et al* (2009).[4] For the sensitivity and specificity values, the high and low values used in the sensitivity analysis were the 95% confidence intervals reported in the PALOH study.[18] For the utility values, the high and low values for the sensitivity analysis were the 95% confidence intervals from the original studies from which the values were sourced.

For the parameter related to the probability of AIHL for neonates with the m.1555A>G variant prescribed with aminoglycosides, the lower bound estimate (0.3) was taken from Gopel *et al* (2014), a prospective cohort study in a German population.[6] For the other parameters (including all of the cost parameters), reasonable high and low values were chosen to explore the potential uncertainty related to these parameters.

5.9 Model Results

5.9.1 Base-case results

Using the parameters shown in Section 5.7, the base-case results from the early economic model are shown in **Error! Reference source not found.** for the cases of AIHL avoided and Table 21 for QALYs. In terms of AIHL, the results show that using the Genedrive MT-RNR1 ID Kit is estimated to be cost saving over the lifetime of the neonate tested for the m.1555A>G genetic variant with the Genedrive MT-RNR1 ID Kit.

In terms of cost of per QALY, the results show that the Genedrive MT-RNR1 ID Kit dominates the current standard of care over the lifetime, as it is less costly and more effective (**Error! Reference source not found.**).

Table 20 Base-case economic analysis – cases of AIHL avoided (Genedrive MT-RNR1 ID Kit vs Normal standard of care)

Strategy	Total costs (£)	Cases of AIHL	Incremental cost (£)	Incremental AIHL avoided	ICER (£)
GeneDrive MT-RNR1 ID Kit	136.82	0	-62.61	0.0019	Dominant
Normal standard of care	199.43	0.0019			
Source: Produced by EAG					

Table 21 Base-case economic analysis - QALYs gained (Genedrive MT-RNR1 ID Kit vs Normal standard of care)

Strategy	Total costs (£)	Total QALYs	Incremental cost (£)	Incremental QALYs	ICER (£)
Genedrive MT-RNR1 ID Kit	136.82	23.12	-62.61	0.01	Dominant

Normal standard of care	199.43	23.11			
Source: Produced by EAG					

The results from the deterministic sensitivity analysis are presented in a Tornado plot (**Error! Reference source not found.**). The Tornado shows the impact of the high and low parameter values specified in Tables 14 – 18 on the estimated ICER.

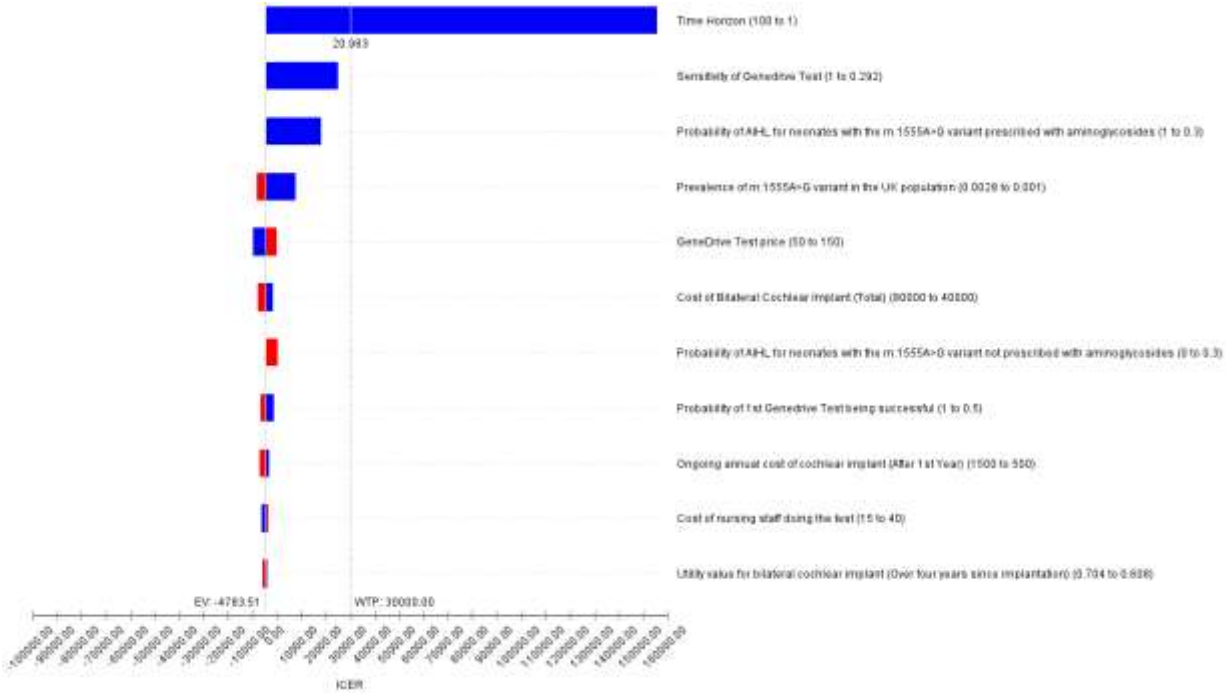

Figure 1 Tornado Diagram Genedrive MT-RNR1 ID Kit pathway vs. Standard pathway

As shown in **Error! Reference source not found.**, the parameter values which have the largest impact on the ICER are the time horizon of the model, the sensitivity of the Genedrive MT-RNR1 ID Kit, the probability of neonates with the m.1555A>G variant prescribed with aminoglycosides suffering from AIHL, the prevalence of the m.1555A>G variant across the population and the cost of the Genedrive MT-RNR1 ID Kit. As **Error! Reference source not found.** shows, varying other parameter values (for example the utility values associated with bilateral cochlear implants and the probability of cochlear implants being successful) did not appear to materially impact the incremental cost per QALY.

The sensitivity of the results to the time horizon reflects the fact that from an NHS resource use perspective, there are significant costs required in order to identify one neonate with the m.1555A>G variant, while the benefits (specifically cost savings related to cochlear implants avoided and utility gains from avoiding AIHL) are likely to only be felt in the medium to long-term. The sensitivity of the results to the time horizon reflects the fact that from an NHS resource use perspective, there are significant costs required in order to identify one neonate with the m.1555A>G variant, while the benefits (specifically cost savings related to cochlear implants avoided and utility gains from avoiding AIHL) are likely to only be felt in the medium to long-term. Table 22 illustrates this by showing the impact on cost-effectiveness of varying the time horizon between one, ten and 50 years. As shown in Table 22, although the Genedrive MT-RNR1 ID Kit has a very large ICER when compared to normal

standard of care for a one-year time horizon, the Genedrive MT-RNR1 ID Kit dominates the current normal standard of care when using both a ten-year and a 50-year time horizon.

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Table 1 Base-case economic analysis: QALYs gained for different time horizons (Genedrive MT-RNR1 ID Kit vs Normal standard of care)

Time Horizon	Strategy	Total costs (£)	Total QALYs	Incremental cost (£)	Incremental QALYs	ICER (£)
One Year Time Horizon	Genedrive MT-RNR1 ID Kit	136.82	0.90	136.46	0.00	148,111
	Normal standard of care	0.36	0.90			
Ten Year Time Horizon	Genedrive MT-RNR1 ID Kit	136.82	7.78	-6.47	0.01	Dominant
	Normal standard of care	143.29	7.77			
50 Year Time Horizon	Genedrive MT-RNR1 ID Kit	136.82	20.42	-53.06	0.01	Dominant
	Normal standard of care	189.88	20.41			
Source: Produced by EAG						

The sensitivity of the results to the time horizon reflects the fact that from an NHS resource use perspective, there are significant costs required in order to identify one neonate with the m.1555A>G variant, while the benefits (specifically cost savings related to cochlear implants avoided and utility gains from avoiding AIHL) are likely to only be felt in the medium to long-term. Table 22 illustrates this by showing the impact on cost-effectiveness of varying the time horizon between one, ten and 50 years. As shown in Table 22, although the Genedrive MT-RNR1 ID Kit has a very large ICER when compared to normal standard of care for a one-year time horizon, the Genedrive MT-RNR1 ID Kit dominates the current normal standard of care when using both a ten-year and a 50-year time horizon.

The impact of the sensitivity of Genedrive MT-RNR1 ID Kit on the cost-effectiveness results reflects the fact that the real-world sensitivity of the Genedrive Test (as reported in the PALOH study[18]) is highly uncertain due to the very small number of positive cases. This uncertainty was reflected in the reported wide confidence intervals used as the high and low values in the deterministic sensitivity analysis.

The sensitivity of the results to the proportion of neonates with m.1555A>G variant suffering from AIHL after being exposed to aminoglycosides reflects the inherent uncertainty related to this parameter. As discussed in Section 1.1.1, although there is clear evidence that m.1555A>G variant is a risk factor for AIHL, most evidence comes from case-control studies which may overestimate this risk, and therefore the precise level of this risk is unknown.

With respect to the results being sensitive to the prevalence of the m.1555A>G variant across the population, this parameter affects how many neonates need to be tested to detect a single neonate with the m.1555A>G variant. As the probability increases, fewer neonates need to incur the cost of testing to detect a neonate with the variant and hence cost-effectiveness of using the Genedrive MT-RNR1 ID Kit improves. Although no data were available to consider how cost-effectiveness varied by different

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Appendix C

A list of excluded records

Parker J, Wright D. Terrible choices in the septic child: a response to the PALOH trial round table authors. Journal of Medical Ethics 2021;47:114-116. (exclusion reason: wrong publication type)

McDermott JH, Mahood R, Stoddard D, et alPharmacogenetics to Avoid Loss of Hearing (PALOH) trial: a protocol for a prospective observational implementation trial. BMJ Open 2021;11:e044457. (exclusion reason: wrong publication type)

McDermott JH. Genetic testing in the acute setting: a round table discussion. Journal of Medical Ethics 2020;46:531-532. (exclusion reason: wrong publication type)

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Phillips LL, Glindzicz MB, Lench N, et al. The future role of genetic screening to detect newborns at risk of childhood-onset hearing loss. International Journal of Audiology. 2013; 52(2), 124-133. (exclusion reason: wrong publication type)

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Zhu Q, Li M, Zhuang X, et al. Assessment of Hearing Screening Combined With Limited and Expanded Genetic Screening for Newborns in Nantong, China. JAMA Network Open. 2021; 4(9):e2125544. (exclusion reason: wrong index test)